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14. ABSTRACT

The goal of this project is to use national Veterans Affairs (VA) healthcare data to determine the benefits and risks of use of antipsychotic medications to augment first-line medication therapy in patients with posttraumatic stress disorder (PTSD). To date, over 2.5 million American men and women have served in support of the military operations in Iraq and Afghanistan. PTSD is the most commonly diagnosed mental health disorder in Veterans, with nearly 1 in 3 returning Iraq and Afghanistan Veterans seen in VA care receiving this diagnosis. In addition to counseling therapies, several medications are effective in treating PTSD symptoms. However, clinical trials show less than 30% of patients will achieve remission of PTSD symptoms with these treatments. Therefore, providers and patients will look for additional medications to augment therapy. Antipsychotic medications are FDA-approved and beneficial for the treatment of bipolar disorder and psychotic disorders, such as schizophrenia. However, they have been increasingly prescribed "off-label" for non-approved conditions, such as PTSD. In a prior study, we found that 1 in 5 returning Iraq and Afghanistan Veterans with PTSD seen in VA care were receiving an antipsychotic medication in the absence of one of the approved conditions. This is occurring despite VA and DoD guidelines that discourage the use of antipsychotics for PTSD treatment because there is still considerable debate about whether antipsychotic medications are safe and effective in PTSD. This project uses the VA healthcare data of Veteran's with PTSD to compare the effects of antipsychotics versus other types of psychiatric medications to determine metabolic and mental health outcomes, as well as gender and racial differences in the risks and benefits of antipsychotic use.

15. SUBJECT TERMS
PTSD, treatment augmentation, antipsychotic medication, mental health hospitalization, suicidality screening, metabolic disease, cardiovascular disease

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1. INTRODUCTION:

The goal of this project is to use national Veterans Affairs (VA) healthcare data to determine the benefits and risks of use of antipsychotic medications to augment first-line medication therapy in patients with posttraumatic stress disorder (PTSD). To date, over 2.5 million American men and women have served in support of the military operations in Iraq and Afghanistan. PTSD is the most commonly diagnosed mental health disorder in Veterans, with nearly 1 in 3 returning Iraq and Afghanistan Veterans seen in VA care receiving this diagnosis. In addition to counseling therapies, several medications are effective in treating PTSD symptoms. However, clinical trials show less than 30% of patients will achieve remission of PTSD symptoms with these treatments. Therefore, providers and patients will look for additional medications to augment therapy. Antipsychotic medications are FDA-approved and beneficial for the treatment of bipolar disorder and psychotic disorders, such as schizophrenia. However, they have been increasingly prescribed “off-label” for non-approved conditions, such as PTSD. In a prior study, we found that 1 in 5 returning Iraq and Afghanistan Veterans with PTSD seen in VA care were receiving an antipsychotic medication in the absence of one of the approved conditions. This is occurring despite VA and DoD guidelines that discourage the use of antipsychotics for PTSD treatment because there is still considerable debate about whether antipsychotic medications are safe and effective in PTSD. This project uses the VA healthcare data of Iraq and Afghanistan Veteran’s with PTSD to compare the effects of antipsychotics versus other types of psychiatric medications to determine metabolic and mental health outcomes, as well as gender and racial differences in the risks and benefits of antipsychotic use.

2. KEYWORDS:

PTSD, treatment augmentation, antipsychotic medication, mental health hospitalization, suicidality screening, metabolic disease, cardiovascular disease

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?** The overall Aims for this project are:
  - Aim 1: To determine the metabolic impact of augmentation of first-line serotonin reupdate inhibitor (SRI) treatment with antipsychotics versus other psychiatric medications if OEF/OIF/OND Veterans with posttraumatic stress disorder (PTSD)

- Aim 2: To determine the impact of augmentation of first-line SRI treatment with antipsychotics versus other psychiatric medications on PTSD symptoms and mental health outcomes in OEF/OIF/OND Veterans with PTSD
- Aim 3: To examine variations in the risks and benefits of augmentation of first-line SRI treatment with antipsychotics versus other psychiatric medications in specific demographic subgroups

The specific tasks from the Statement of Work relevant to this reporting period include:

Task 1: Obtain Local Institutional Review Board and DoD Human Research Protection Office approvals. Timeline- months 1-3. Status: completed.

Task 2: Obtain and merge VA and DoD datasets for project. Timeline- months 3-4. Status: completed.

Task 3: Clean and code VA and DoD data for all project Aims. Timeline- months 3-6. Status: completed.

Task 6: Complete primary analyses and hypothesis testing for Aim 2, including comparing effects of augmentation of first-line therapy with antipsychotics versus other psychiatric medications on mental health outcomes. Timeline- months 13-15. Status: completed except for propensity score adjusted models.

- **What was accomplished under these goals?**

Cleaning data and creating an analytic dataset (Tasks 1-3 on Statement of Work)

We spent a significant portion of this reporting period creating our analytic dataset. Our project uses national VA electronic healthcare data, which is collected for administrative and not research purposes. Therefore, nearly every variable needs to be extensively cleaned. For our pharmacy data, we have highly specific inclusion criteria to define PTSD treatment augmentation, including use of a first-line PTSD medication for at least 60 days, addition of one of the selecting augmenting medications, continued use of that medication for at least 60 days during a 120 period. This required cleaning the pharmacy data so we could determine the type and amount of psychiatric medication each patient was on in each calendar day from 2007-2015. We were able to create such a calendar using information on pharmacy refills but needed to account for natural irregularities in patients' refill patterns, such as requesting a refill before a prior prescription had been finished or changing doses in medication. We created a system to calculate reserved medication that patients would have and to allow them to use this during "gaps" in prescription fills.

Similar detailed cleaning needed to be done for our outcomes. For example, we will be looking at changes in lipid levels, hemoglobin A1c, and glucose. For each of these lab tests, each VA site can name them something different and can change names over times. Labs should be linked to Logical Observation Identifiers Names (LOINC) codes, an international standard system that assigns a numeric code to specific lab tests. However, VA data quality reports have found that LOINCs are sometimes assigned incorrectly and a substantial portion of labs are not linked to LOINC codes. Therefore, to clean labs, we needed to search by keyword and LOINC and then review the characteristics of each test (sample type, reference ranges, actual ranges from data) to ensure they were correct. As an example, this required reviewing over 14,000 potential labs test name/LOINC combinations for glucose. A similar process was completed for the other labs used in this project. Though our Aim 1 was to examine cardiometabolic outcomes, given the length of time required to review the lab data, while we cleaned these outcomes, we began our analyses for our Aim 2 (mental health outcomes). Therefore, we will be reporting results for Aim 2 prior to Aim 1. We do not anticipate overall delays to the project. We informed our Senior Science Officer, Dr. Rahul Thakar, of this change in August 2017. We believe the time invested in this extensive cleaning has been very valuable as we now have high confidence in the quality of our data. We are also sharing our methods with other VA investigators.

Comparing characteristics of patients receiving antipsychotic versus non-antipsychotic medication.

As shown in Table 1 below, we examined a number of characteristics of patients and the facilities where they received care that could potentially affect the augmenting medication received and our outcomes of interest. Given our large sample size, we found many statistically significant differences in these characteristics. However, the majority of these differences were small and not clinically significant. In terms of demographics and comorbidities, those prescribed antipsychotics were more likely to be white and to have comorbid major depressive disorder and alcohol abuse/dependence. Also, as expected from our prior research, in this population of patients with PTSD, we observed rates of cardiovascular risk factors that are higher that we would expect given the young age of the population. However, rates were similar in those prescribed antipsychotics or other augmenting medications. Prescribing facility and service utilization factors were also similar except for mental health utilization where those prescribed antipsychotics had on average 5 more mental health visits in the year prior to treatment augmentation than those prescribed non-antipsychotics.

Table 1: Characteristics by augmenting medication group

Variable	**AAP (N=24,131) N (column %)**		**NAP (N=96,383) N (column %)**		**P-value**
Sociodemographic					
Age, Mean ± SD	35.1	± 8.9	35.7	± 9.0	<.0001
Birth sex					<.0001
Male	21,823	(90.4)	85,822	(89.0)	
Female	2,308	(9.5)	10,561	(11.0)	
Race					<.0001
White	18,581	(77.0)	71,091	(73.8)	
Black	3,537	(14.7)	16,089	(16.7)	
Other	2013	(8.3)	9,203	(9.6)	
Ethnicity					0.0202
Hispanic	2,645	(11.0)	10,865	(11.3)	
Non-Hispanic	20,931	(86.7)	83,046	(86.2)	
Unknown	555	(2.3)	2,472	(2.6)	
Marital Status					0.0051
Married	13,066	(54.2)	53,275	(55.3)	
Never Married	5,399	(22.4)	20,854	(21.6)	
Other	5,666	(23.5)	22,254	(23.1)	
Comorbidities					
Major Depressive Disorder	9,013	(37.6)	31,672	(32.9)	<.0001
Personality Disorder	1,579	(6.5)	3,850	(4.0)	<.0001

Generalized Anxiety Disorder	1,869	(7.6)	6,921	(7.2)	0.0026
Insomnia	5,931	(24.6)	23,326	(24.2)	0.2219
Substance abuse/dependence	9,697	(40.2)	33,545	(43.8)	<.0001
Alcohol abuse/dependence	8,079	(33.5)	28,468	(29.5)	<.0001
Traumatic Brain Injury	4,193	(17.4)	15,514	(16.1)	<.0001
Obesity	5,487	(22.7)	22,092	(22.9)	0.5458
Dyslipidemia	7,994	(33.1)	32,027	(33.2)	0.7649
Diabetes	1,156	(4.8)	4,995	(5.2)	0.0134
Hypertension	6,393	(26.5)	25,352	(26.3)	0.5501
Heart disease (myocardial infarction or ischemic heart disease or unstable angina)	164	(0.7)	585	(0.6)	0.1989
Congestive Heart Failure	77	(0.3)	291	(0.3)	0.6655
Cerebrovascular disease	47	(0.2)	205	(0.2)	0.5857
Charlson Comorbidity Index score	0.303	± 0.7	0.296	± 0.7	0.1439
Prescribing Facility Factors					
VA Prescribing Site					0.0286
Medical Center	14,956	(62.0)	58,997	(61.2)	
Community-Based Outpatient Clinics	9,175	(38.0)	37,386	(38.8)	
Service Utilization factors					

Primary Care utilization (# visits in pre-index year)	3.2	± 3.2	3.0	± 2.9	<.0001
Mental Health utilization (# visits in pre-index year)	21.7	± 33.9	16.88	± 28.0	<.0001
Drive time to nearest VA at time of index Rx (minutes)*	22.9	± 17.9	22.8	± 24.3	0.4890
VA Service Connection % Mean ± SD	54.1	± 35.0	52.7	± 34.7	<.0001

* missing 153

**Numbers for the individual non-antipsychotics are: Buspirone 9,211, Mirtazapine 11,232, Mood Stabilizers 12,260, Nefazodone 39, Prazosin 28,571, Trazodone 30,243, and Tricyclics 4,827

Changes in PTSD symptom scores by augmenting medication type

For our main analyses, we define the day the patient started the augmenting medication as the "index date". We then compare outcomes from the year prior to the index date to the year following the index date to evaluate the effect of the augmenting medication. We found that patients in all augmenting medication groups had minimal improvement in their PTSD symptoms from the year prior to receiving the augmenting medication to the year after (Table 2a). Improvements in PTSD symptoms did not differ between those on antipsychotics versus non-antipsychotics (Table 2b). Adjusting for the factors shown in Table 1 did not substantially change our findings. From our prior work and published studies of these medications, we expected to find no or modest improvement in PTSD symptoms given these are patients that are not responding to first line therapies and may be more difficult to treat. However, in our sensitivity analyses, we will also examine doses and time on individual medications. We may find that patients on higher doses or taking medications over a longer period have greater benefit. We can also compare characteristics of treatment responders and non-responders to see if these medications may have efficacy in specific subgroups. If we do not find overall benefit on PTSD symptoms, this is extremely important as many of these drugs have adverse cardiovascular and metabolic consequences, and we may be putting patients at risk without a substantial benefit on their symptoms. We are also currently conducting propensity score

matched analyses. However, as we found few substantial differences in our Table 1 characteristics, we expect our findings will be similar to our fully adjusted models. Finally, our co-Investigator on this grant, Dr. Shira Maguen, has worked with experts at the Salt Lake City VA to develop a natural language processing algorithm to extract PTSD Checklist Scores from text notes in the medical chart. At this point, we have only been able to access PTSD symptom scores that were entered through the VA Mental Health Assistant software. Dr. Maguen has found that many providers are entering symptom scores in chart progress notes rather than the software. Therefore, we plan to use the algorithm she has developed to extract additional scores. We will then repeat our analyses and report updated findings.

Table 2a: Changes in PTSD Checklist scores by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	62.72	61.88	-0.83	<0.0001	-1.33%
Non-antipsychotics	60.98	60.14	-0.84	<0.0001	-1.38%
By Class					
Buspirone	60.91	60.30	-0.61	0.0052	-1.00%
Mirtazapine	61.73	60.97	-0.76	<0.0001	-1.24%
Mood Stabilizers	62.37	61.52	-0.85	<0.0001	-1.36%
Prazosin	61.98	61.01	-0.96	<0.0001	-1.55%
Trazodone	60.65	59.82	-0.83	<0.0001	-1.37%
Tricyclics	62.08	61.13	-0.95	0.002	-1.53%

***Note we have removed nefazodone as the group size was very small**

Table 2b: Unadjusted and adjusted models for change in PTSD Checklist symptom scores in non-antipsychotic vs. antipsychotic medications.

Table shows the coefficient for the difference in changes from the pre- to post-index year compared to the reference group of antipsychotics with p-value in ().

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4
Non-antipsychotics	-0.038 (0.75)	-0.033 (0.79)	-0.041 (0.74)	-0.043 (0.72)	-0.050 (0.69)
By Class					
Buspirone	0.26 (0.28)	0.25 (0.28)	0.23 (0.32)	0.23 (0.32)	0.23 (0.34)
Mirtazapine	0.05 (0.83)	0.06 (0.77)	0.06 (0.77)	0.06 (0.77)	0.05 (0.81)
Mood Stabilizers	0.03(0.90)	0.03 (0.90)	0.02 (0.92)	0.02 (0.92)	0.01 (0.95)
Prazosin	-0.15 (0.36)	-0.13 (0.45)	-0.14 (0.39)	-0.15 (0.36)	-0.15 (0.34)
Trazodone	-0.01 (0.94)	-0.005 (0.98)	-0.02 (0.92)	-0.02 (0.91)	-0.03(0.86)
Tricyclics	-0.19 (0.55)	-0.17 (0.60)	-0.17 (0.55)	-0.19 (0.55)	-0.20 (0.52)

Model 1: Adjusted for sociodemographics (see Table 1)

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

As a secondary mental health outcome, we examined changes in the Primary Care PTSD screen (a 4-item questionnaire that is mandated in periodic assessments in VA). Similar to the PTSD checklist, we found small improvements in most groups from the pre- to post-index year without differences in antipsychotics versus non-antipsychotic medications.

Table 2c: Changes in Primary Care PTSD Screen scores by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	1.17	1.15	-0.02	0.0006	-1.97%
Non-antipsychotics	1.13	1.12	-0.01	0.004	-0.94%
By Class					
Buspirone	1.10	1.07	-0.02	0.06	-2.21%
Mirtazapine	1.13	1.10	-0.02	0.03	-2.08%
Mood Stabilizers	1.16	1.14	-0.02	0.07	-1.50%
Prazosin	1.17	1.18	0.01	0.18	0.70%
Trazodone	1.10	1.09	-0.01	0.22	-0.77%
Tricyclics	1.13	1.10	-0.03	0.05	-2.77%

Table 2d: Unadjusted and adjusted models for change in Primary Care PTSD Screen scores in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4
Non-antipsychotics	0.012 (0.11)	0.012 (0.12)	0.012 (0.14)	0.011 (0.15)	0.010 (0.19)
By Class					
Buspirone	-0.001 (0.93)	0.00007 (0.99)	0.0007 (0.96)	0.0005 (0.97)	0.001 (0.94)
Mirtazapine	-0.0005 (0.97)	-0.001 (0.93)	-0.002 (0.87)	-0.002 (0.87)	-0.002 (0.87)
Mood Stabilizers	0.0056 (0.64)	0.0057 (0.63)	0.0057 (0.64)	0.0057 (0.64)	0.0053 (0.66)
Prazosin	0.031 (0.001)	0.030 (0.002)	0.029 (0.002)	0.028 (0.003)	0.026 (0.007)

Trazodone	0.014 (0.12)	0.014 (0.14)	0.013 (0.16)	0.013 (0.18)	0.012 (0.20)
Tricyclics	-0.008 (0.61)	-0.007 (0.66)	-0.006 (0.72)	-0.006 (0.71)	-0.007 (0.66)

Model 1: Adjusted for sociodemographics (see Table 1)

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Changes in mental health emergency room visits and hospitalizations by augmenting medication type

We used ICD-9 and 10 codes to identify emergency room visits and hospitalizations with a primary diagnosis that was for a mental health condition. For each medication group, we determined the difference between the rate in the pre- and post-index years. We found patients in the antipsychotic group had the greatest number of mental health emergency room visits in the pre-index year, followed by mood stabilizers and mirtazapine (Table 3a). All groups apart from tricyclics had significant declines in their rates of hospitalization. In fully adjusted models, patients augmented with trazodone or tricyclic antidepressants had significantly smaller improvements in mental health emergency room visits than patients augmented with antipsychotics. Findings for mental health hospitalizations were similar with the highest burden of hospitalizations pre-augmentation in the antipsychotic group (Table 3c) and all groups except those prescribed tricyclic antidepressants having significantly lower rates of hospitalization in the post-index year. In fully adjusted models, patients receiving augmentation with prazosin, trazodone, or tricyclic antidepressants had significantly smaller improvements in hospitalization than those prescribed antipsychotics (Table 3d).

Table 3a Changes in Mental Health Emergency Room visits by augmenting medication group

Rates are shown as # visits/100 person years

Medications	Pre-Index Year	Post-Index Year	Absolute Change (post minus pre)	P-value	Percent Change (post minus pre)
Antipsychotics	24	19	-6	<0.0001	-23.0%
Non-antipsychotics	16	13	-3	<0.0001	-18.6%

By Class					
Buspirone	18	15	-3	0.0002	-18.9%
Mirtazapine	20	16	-4	<0.0001	-19.2%
Mood Stabilizers	20	14	-5	<0.0001	-27.3%
Prazosin	16	13	-3	<0.0001	-17.8%
Trazodone	15	12	-2	<0.0001	-15.5%
Tricyclics	10	9	-1	0.45	-6.8%

Table 3b: Unadjusted and adjusted models for change in Mental Health Emergency Room visits in non-antipsychotic vs. antipsychotic medications

Table shows the coefficient for the difference in changes from the pre- to post-index year compared to the reference group of antipsychotics with p-value in ().

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Non-antipsychotics	2.5 (0.12)	1.8 (0.10)	1.0 (0.07)	0.9 (0.07)	0.8 (0.05)
By Class					
Buspirone	2.1 (0.42)	1.6 (0.40)	1.0 (0.35)	0.8 (0.34)	0.7 (0.30)
Mirtazapine	1.8 (0.40)	1.3 (0.38)	0.8 (0.33)	0.7 (0.33)	0.5 (0.29)
Mood Stabilizers	1.4 (0.31)	0.7 (0.29)	-0.2 (0.24)	-0.1 (0.24)	-0.2(0.20)
Prazosin	2.7 (0.15)	1.9 (0.14)	1.1 (0.10)	0.9 (0.10)	0.8 (0.07)
Trazodone	3.3 (0.04)	5.5 (0.03)	3.8 (0.02)	3.1 (0.02)	3.4 (0.009)
Tricyclics	4.9 (0.07)	3.7 (0.06)	2.5 (0.04)	2.2 (0.04)	2.2 (0.02)

Table 3c Mental Health Hospitalizations by augmenting medication group

Medications	**Pre-Index Year**	**Post-Index Year**	**Absolute Change (post minus pre)**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	29	22	-7	<0.0001	-24.6%
Non-antipsychotics	19	15	-4	<0.0001	-18.6%

By Class					
Buspirone	20	15	-5	<0.0001	-24.5%
Mirtazapine	23	18	-5	<0.0001	-21.3%
Mood Stabilizers	24	18	-6	<0.0001	-24.8%
Prazosin	19	16	-4	<0.0001	-18.3%
Trazodone	16	14	-2	<0.0001	-12.2%
Tricyclics	12	11	-1	0.15	-10.8%

Table 3d: Unadjusted and adjusted models for change in Mental Health Hospitalizations in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Non-antipsychotics	3.6 (0.007)	2.6 (0.006)	1.5 (0.003)	1.3 (0.003)	1.2 (0.0009)
By Class					
Buspirone	2.1 (0.97)	1.5 (0.97)	0.8 (0.97)	0.6 (0.97)	0.5 (0.97)
Mirtazapine	0.2 (0.36)	0.2(0.34)	0.1 (0.30)	0.1 (0.30)	0.1 (0.26)
Mood Stabilizers	0.1 (0.96)	0.1 (0.96)	0.3 (0.96)	0.3 (0.96)	0.2 (0.96)
Prazosin	3.7(0.029)	2.7 (0.024)	1.5 (0.014)	1.3 (0.014)	1.2 (0.007)
Trazodone	5.2 (<.0001)	3.8 (<.0001)	2.3 (<.0001)	2.0 (<.0001)	2.0 (<0.0001)
Tricyclics	5.9 (0.04)	4.3 (0.04)	2.7 (0.02)	2.3 (0.02)	2.2 (0.01)

Changes in suicidal ideation and plan

We used responses on the VA-mandated annual suicidality screen to examine the proportion of patients screening positive for suicidal ideation in each augmenting group over time. Patients prescribed antipsychotics had the highest rates of suicidal ideation in the pre-index year, with nearly one in four endorsing suicidal ideation (Table 4a). Most groups had significant improvements in suicidal ideation after treatment augmentation, though in adjusted models, the improvements did not differ between those prescribed antipsychotics versus other types of psychiatric medications (Table 4b). We also examined the proportion screened who endorsed having a suicidal plan. This was highest among those augmented with antipsychotics. In contrast to suicidal ideation, none of the groups had significant reductions in endorsement of suicidal plan after treatment augmentation (Table 4c).

Table 4a: Changes in Proportion of those Screened with Positive Suicidal Ideation by augmenting medication group.

Medications	Pre-Index Year	Post-Index Year	Absolute Change (post minus pre)	P-value
Antipsychotics	22.5%	20.9%	-1.6%	0.009
Non-antipsychotics	18.1%	16.9%	-1.3%	<0.0001
By Class				
Buspirone	17.4%	15.3%	2.1%	0.02
Mirtazapine	19.3%	18.8%	-0.5%	0.59
Mood Stabilizers	19.6%	18.3%	-1.3%	0.11
Prazosin	18.5%	17.2%	-1.3%	0.01
Trazodone	17.0%	15.7%	-1.3%	0.009
Tricyclics	17.0%	16.3%	-0.7%	0.41

Table 4b: Unadjusted and adjusted models for change in Positive Suicidal Ideation in non-antipsychotic vs. antipsychotic medications.

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4
Non-antipsychotics	0.32 (0.89)	0.29 (0.92)	0.25 (0.90)	0.24 (0.93)	0.17 (0.99)
By Class					
Buspirone	-0.49 (0.44)	-0.47 (0.45)	-0.41 (0.51)	-0.39 (0.52)	-0.39 (0.54)
Mirtazapine	1.13 (0.34)	1.14 (0.33)	1.14 (0.31)	1.08 (0.33)	0.97 (0.38)
Mood Stabilizers	0.29 (0.89)	0.25 (0.92)	0.24 (0.91)	0.23 (0.91)	0.12 (0.99)
Prazosin	0.30 (0.91)	0.24 (0.96)	0.15 (0.99)	0.14 (0.97)	0.04 (0.88)
Trazodone	0.25 (0.93)	0.22 (0.92)	0.21 (0.97)	0.17 (0.93)	0.14 (0.92)
Tricyclics	0.58 (0.82)	0.54 (0.83)	0.36 (0.90)	0.36 (0.91)	0.32 (0.91)

Model 1: Adjusted for sociodemographics (see Table 1)

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Table 4c: Changes in Proportion of those Screened with Positive Suicidal Plan by augmenting medication group.

Medications	Pre-Index Year	Post-Index Year	Absolute Change (post minus pre)	P-value
Antipsychotics	12%	10.8%	-1.3%	0.13
Non-antipsychotics	10.2%	10.0%	-0.2%	0.65
By Class				
Buspirone	9.1%	8.0%	-1.0%	0.41
Mirtazapine	11.2%	10.3%	-0.9%	0.45
Mood Stabilizers	11.3%	9.7%	-1.7%	0.15
Prazosin	10.2%	10.8%	06%	0.43
Trazodone	9.7%	10.0%	0.4%	0.63
Tricyclics	10.8%	9.7%	-1.1%	0.55

- **What opportunities for training and professional development has the project provided?**
  Nothing to report at this time though we anticipate involving trainees to participate in the dissemination of study findings once analyses are complete.
- **How were the results disseminated to communities of interest?**
  Nothing to report. This project is currently in the analysis stage. As such, no results are currently available. Accomplishments, impact, and products will be more thoroughly discussed in future stages of the project.
- **What do you plan to do during the next reporting period to accomplish the goals?**
  During the next reporting period we will complete our sensitivity analyses for Aim 2 (mental health outcomes), including using a natural language processing algorithm to extract additional PTSD symptom scores as described above. We will also complete our analyses for Aims 1 (metabolic/cardiovascular outcomes) and 3 (examination of demographic subgroups). This will provide a fuller picture of the risks and benefits of treatment augmentation. If as we anticipate, antipsychotic medications are associated with adverse cardiovascular and metabolic consequences, they may not be appropriate for augmentation

given the minimal improvements we found in mental health outcomes compared with other types of augmenting medications.

4. IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**
  Nothing to report
- **What was the impact on other disciplines?**
  Nothing to report
- **What was the impact on technology transfer?**
  Nothing to report
- **What was the impact on society beyond science and technology?**
  Nothing to report

5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**
  As described above, we reversed the order of completion of Aims 1 and 2 due to additional time required to clean the data for Aim 1. We informed Dr. Thakar, the Senior Science Officer on this project, of this change via email in August 2017.

Actual or anticipated problems or delays and actions or plans to resolve them

Though we reversed the order of Aims 1 and 2 we do not anticipate any delays on overall project completion. Cleaning this complex administrative data did take additional time as we found errors in coding and classification that needed to be corrected. Therefore, we are still completing some sensitivity analyses for our examination of mental health outcomes. Again, we do not believe there will be any delays in overall completion.

- **Changes that had a significant impact on expenditures**
  None
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
  None
- **Significant changes in use or care of human subjects**
  None
- **Significant changes in use or care of vertebrate animals.**
  None

- **Significant changes in use of biohazards and/or select agents**

  None

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  We will be presenting preliminary data from this project at the International Society of Traumatic Stress Studies annual meeting on November 10, 2017 as part of a symposium entitled Complicated Prescribing Practices in VA Patients with PTSD: Approaches to Observation and Improvement.

- **Journal publications.**

  Nothing to report

- **Books or other non-periodical, one-time publications.**

  Nothing to report

- **Other publications, conference papers, and presentations.**

  Nothing to report

- **Website(s) or other Internet site(s)**

  None

- **Technologies or techniques**

  None

- **Inventions, patent applications, and/or licenses**

  None

- **Other Products**

  None

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	*Beth Cohen, MD, MAS*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	2.4
Contribution to Project:	*Dr. Cohen has overall scientific and administrative responsibility for this project and supervises all project staff.*
Funding Support:	*VA, PCORI, UCSF*

Name:	*Karen Seal, MD, MPH*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.2
Contribution to Project:	*Dr. Seal has assisted with planning data analyses and interpreting findings for the proposed project.*
Funding Support:	*NCIRE, UCSF*

Name:	*Thomas Neylan, MD*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.2

Contribution to Project:	*Dr. Neylan has provided guidance on coding of metabolic outcomes as well as examination of specific psychiatric medication classes and doses.*
Funding Support:	*VA, UCSF*

Name:	*Shira Maguen, PhD*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.2
Contribution to Project:	*Dr. Maguen has assisted in data cleaning, coding, and interpretation for these outcomes.*
Funding Support:	*VA, UCSF*

Name:	*Anne Woods*
Project Role:	*Data Analyst/Data Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	*Ms. Woods is responsible for data extraction, cleaning and error checking and running all study analyses.*

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  Nothing to Report
- **What other organizations were involved as partners?** *Not applicable*

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** *Not applicable*
- **QUAD CHARTS:** *Not applicable*

9. APPENDICES: *Not applicable*